ANNEX 13

MANUFACTURE OF INVESTIGATIONAL MEDICINAL PRODUCTS

Introduction

Medicinal products intended for research and development trials are not at present subject either to marketing or manufacturing Community legislation.

However, when adopting Directive 91/356/EEC on GMP for medicinal products for human use, it was agreed to include a "whereas" stating that Member States may require compliance with the principles of GMP during the manufacture of products intended for use in clinical trials. It was also suggested in a EC Discussion Paper (III/3044/91) in January 1991 that it is illogical for experimental products not to be subject to the controls which would apply to the formulations of which they are the prototypes and most of the comments received from interested parties were in line with this suggestion.

Therefore it was agreed to prepare this annex to the Community Guide to Good Manufacturing Practice so that both those Member States instituting controls voluntarily and manufacturers of investigational products would have a reference point to enable common standards to evolve in all Member States.

The Commission is currently preparing a draft directive on clinical trials and this first revision of the annex will be reviewed when necessary.

Although veterinary investigational medicinal products should also be prepared under appropriate GMP conditions, most aspects of this annex derive from human GCP and are thus specific to investigational medicinal products for human use.

Note

The principles and many of the detailed guidelines of Good Manufacturing Practice for Medicinal Products (Volume IV of the series "The rules governing medicinal products in the European Union") as well as some other guidelines published by the European Commission (e.g. validation of virus inactivation/removal) are relevant to the preparation of products for use in clinical trials.

This annex specifically addresses those practices which may be different for investigational products, which are usually not manufactured under a set routine, and with possibly incomplete characterisation of the product at initial stages of clinical development. It also includes guidance on ordering, shipping, and returning clinical supplies, which is at the interface with the Guideline on Good Clinical Practice (revised 1 January 1997).

Glossary

BLINDING

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

CLINICAL TRIAL

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s) and/or to identify any adverse reactions to an investigational product(s), and /or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy.

COMPARATOR PRODUCT

An investigational or marketed product (i.e., active control), or placebo, used as a reference in clinical trial.

INVESTIGATIONAL MEDICINAL PRODUCT

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Order

Instruction to process, package and/or ship a certain number of units of investigational product.

Product Specification File

Reference file containing all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release and shipping.

SHIPPING/DISPATCH

The operation of packaging for shipment, and sending of ordered medicinal products for clinical trials.

SPONSOR

An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.

Quality management

1. Some of the production processes of investigational medicinal products which have no marketing authorisation may not be validated to the extent necessary for a routine production. For sterile products, the validation of sterilising processes should be of the same standard as for products authorised for marketing. The product specifications and manufacturing instructions may vary during development. This increased complexity in manufacturing operations requires a highly effective system of Quality Assurance.

2. The Quality Assurance System, designed, set up and verified by the manufacturer, should be described in written procedures maintained by the sponsor, taking into account the GMP principles applied to investigational medicinal products.

3. Packaging and labelling operations are often performed after the release of the bulk product and in accordance with specific requirements of different trials. These operations are of paramount importance for the integrity of clinical trials. In this respect, self inspection or independent audits, as referred to in the Community Guideline on Good Clinical Practice and in 9.2. of the Guide to GMP are an integral part of the Quality Assurance system.

Personnel

4. Although it is likely that the number of staff involved will be small, there should be separate people responsible for production and quality control. All production operations should be carried out under control of a clearly identified responsible person. Personnel involved in release of investigational medicinal products should be appropriately trained in quality systems, GMP and regulatory requirements specific to these types of products. They must be independent of the staff responsible for production.

Premises and equipment

5. During manufacture of investigational medicinal products, it may be that different products are handled in the same premises and at the same time, and this reinforces the need to minimise all risks of contamination, including cross-contamination and product mix up, by using appropriate procedures.

6. For the production of the particular products referred to in paragraph 3.6 of the Guide to GMP, campaign working may be acceptable in place of dedicated and self-contained facilities. Because the toxicity of the materials may not be fully known, cleaning is of particular importance; account should be taken of the solubility of the product and of excipients in various cleaning solvents.

7. Validation of aseptic processes presents special problems when the batch size is small; in these cases the number of units filled may be the maximum number filled in production. Filling and sealing is often a hand operation presenting great challenges to sterility so enhanced attention should be given to environmental monitoring.

Documentation

8. Specifications (for starting materials, primary packaging materials, intermediate and bulk products and finished products), manufacturing formulae and processing and packaging instructions may be changed as development of the product progresses. Each new version should take into account the latest data, current technology used and the regulatory and pharmacopoeial requirements, and should refer to the previous version to allow traceability to the previous document. Rationales for changes should be recorded.

9. It may not be necessary to produce Master Formula and Processing Instructions, but for every manufacturing operation or supply there should be clear and adequate written instructions and written records. Records are particularly important for the preparation of the final version of the documents to be used in routine manufacture.

10. Batch manufacturing records should be retained for at least two years after completion of the clinical trial or at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

Order

11. The order may request the processing and/or packaging of a certain number or units and/or their shipping. It may only be given by the sponsor to the manufacturer of an investigational medicinal product. It should be in writing (though it may be transmitted by electronic means), and precise enough to avoid any ambiguity. It should be formally authorised and it should refer to the approved Product Specification File.

Product Specification File

12. All the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release, storage conditions and/or shipping should be referenced in a Product Specification File. This Product Specification File should be continually updated, ensuring appropriate traceability to the previous versions.

Manufacturing Formulae and Processing Instructions

13. Any changes should be carried out according to a written procedure which should address any implications for stability and bioequivalence. Changes should be authorised by a responsible person and be clearly recorded.

Packaging instructions

14. Packaging and labelling of investigational medicinal products are likely to be more complex and more liable to errors (which are also harder to detect) than of marketed products when "blinded" labels are used. Supervision procedures such as label reconciliation, line clearance, etc. and the independent checks by quality control staff should accordingly be intensified.

15. Investigational medicinal products must be packed in an individual way for each patient included in the clinical trial. Packaging instructions are based on the order. Contrary to what happens with large-scale manufacturing of licensed medicinal products, batches of investigational medicinal products may be subdivided into different packaging batches and packaged in several operations over a period of time.

16. The number of units to package should be specified prior to the start of the packaging operations, considering also the number of units necessary for carrying out quality controls and the number of samples to be kept. A reconciliation should take place at the end of the packaging and labelling process.

Labelling instructions

17. Labels should include:

    a) name of the sponsor;

    b) pharmaceutical dosage form, route of administration, quantity of dosage units (and name/identifier of the product and strength/potency in case of open trial);

    c) the batch and/or code number to identify the contents and packaging operation;

    d) the trial subject identification number, where applicable;

    e) directions for use;

    f) "for clinical trial use only";

    g) the name of the investigator (if not included as a code in the trial reference code);

    h) a trial reference code allowing identification of the trial site and investigator;

    i) the storage conditions;

    j) the period of use (use-by date, expiry date or re-test date as applicable), in month/year);

    k) "keep out of reach of children" except when the product is for use only in hospital;

    The outer packaging may include symbols or pictograms to clarify certain information, mentioned above and the request "return empty packaging and unused products".

    Additional information for example any warnings and handling instructions, where applicable may be displayed according to the order. A copy of each type of label should be kept in the batch record.

18. On the immediate packaging when the outer packaging carries the particulars mentioned in paragraph 17, a-k, the particulars mentioned in paragraph 17, a-f, shall be given.

19. When the outer packaging carries the particulars mentioned in paragraph 18, a-k and the immediate packaging takes the form of blister packs or small immediate packaging units such as ampoules on which the particulars mentioned in paragraph 17, a-f can not be displayed, the particulars mentioned in paragraph 17, a, c and d as well as route of administration in case of ampoules, shall at least appear on the immediate packaging.

20. In case of use date extension, an additional label should be affixed to the investigational medicinal product. This additional label should include the new use date and repeat the batch number. It may be superposed on the old use date, but, for quality control reasons, not on the original batch number. This operation may be performed on site by the clinical trial monitor(s) or the clinical trial site pharmacist, in accordance with specific and standard operating procedures and under contract if applicable. The operation should be checked by a second person. Documented evidence of this additional labelling should be available in the trial documentation and in the batch records.

Manufacturing and packaging batch records

21. Manufacturing and packaging batch records should be kept in sufficient detail for the sequence of operations to be accurately traced back. These records should contain any relevant remarks which enhance existing knowledge of the product and allow improvements of the manufacturing operations and justify the procedures used.

Production

Starting materials

22. The consistency of production may be influenced by quality of the starting materials. Their physical and chemical properties should therefore be defined, documented in their specifications and controlled. Specifications for active starting materials should be as comprehensive as possible, given the current state of knowledge. Specifications for both active and non-active starting materials (excipients) should be periodically re-assessed during development and updated as necessary.

23. Detailed information on the quality of active and non-active starting materials should be available in order to recognise and, as necessary, allow for variation of the production.

Manufacturing operations

24. During the development phase, validated procedures may not always be available, which makes it difficult to know in advance the critical parameters and the in-process controls that would help to control these parameters. In these cases, provisional production parameters and in-process controls may usually be deduced from experience with analogues. Careful consideration by key personnel is called for in order to formulate the necessary instructions and to adapt them continually to the experience gained in production.

25. Reconciliation is an essential part of the control of the manufacturing operations. Actual and theoretical yields should be reconciled and any abnormal discrepancy investigated.

26. Where applicable virus inactivation/removal and/or other impurities of biological origin should be no less than for products authorised for marketing. Cleaning procedures should be very stringent and designed in the light of the incomplete knowledge of the toxicity of the investigational product. Where processes such as mixing have not been validated, additional quality control testing may be necessary.

Principles applicable to comparator product

27. In studies whereby an investigational medicinal product is compared with a marketed product, attention should be paid to ensure the integrity and quality of the comparator product (final dosage form, packaging materials, storage conditions, etc.). If significant changes are to be made to the product, data should be available (e.g. stability, comparative dissolution, bioavailability) to prove that these changes do not significantly alter the original quality characteristics of the product.

28. Because the expiry date stated on the original package has been determined for the medicinal product in that particular package and may not be applicable to the product where it has been repackaged in a different container, it is the responsibility of the sponsor, taking into account the nature of the product, the characteristics of the container and the storage conditions to which the article may be subjected, to determine a suitable use-by date to be placed on the label. Such date is not later than the expiry date of the original package. In the absence of stability data or if stability is not followed during the clinical trial such date should not exceed 25% of the remaining time between the date of repackaging and the expiry date on the original manufacturer's bulk container or a six month period from the date the drug is repackaged, whichever is earlier.

Randomisation code

29. Procedures should describe the generation, distribution, handling and retention of any randomisation code used for packaging investigational products.

Blinding operations

30. A system should be implemented to allow for a proper identification of the 'blinded' products. The system, together with the randomisation code and randomisation list must allow proper identification of the product, including any necessary traceability to the codes and batch number of the product before the blinding operation.

31. Samples of blinded investigational medicinal products should be retained.

Quality control

32. As processes may not be standardised or fully validated, end product testing takes on more importance to ensure that each batch meets its specification.

33. Quality control should especially pay attention to the compliance with specifications which bear on the efficacy of medicinal products, namely:

— accuracy of the therapeutic or unitary dose: homogeneity, content uniformity;

— release of active substances: solubility, dissolution time, etc.

— estimation of stability, if necessary in accelerated and stress conditions, determination of the preliminary storage conditions and shelf-life of the product.

When necessary, Quality Control should also verify the similarity in appearance, smell and taste of "blinded" medicinal products.

34. Samples of each batch of product should be retained under the responsibility of either the manufacturer or of the importer which released the batch for use in the EEA. They should be kept in the primary container used for the study or in a suitable bulk container for at least one year beyond the final shelf-life or two years after completion of the clinical trial whichever is the longest. If the sample is not stored in the pack used for the study, stability data should be available to justify the shelf-life in the pack used.

Release of batches

35. Product release is often carried out in two stages, before and after final packaging:

— bulk product assessment: it should cover all relevant factors, including production conditions, results of in-process testing, a review of manufacturing documentation and compliance with the Product Specification File and the Order;

— finished product assessment: it should cover, in addition to the bulk product assessment, all relevant factors, including packaging conditions, results of in-process testing, a review of packaging documentation and compliance with the Product Specification File and the Order.

Free movement

36. Since investigational products are released ("technical green light") by appropriately qualified staff, subsequent analysis after shipping to other Member States is not justified as long as documented evidence is available that appropriate control analysis and product release have taken place in the EEA.

Contract Manufacture and Contract Analysis

37. The contract must clearly state, among other provisions, that the medicinal products are to be used in clinical trials. Co-operation between the contracting parties should be very close.

Complaints

38. The conclusions of any investigation carried out in relation to a complaint should be discussed between the manufacturer and the sponsor (if different) or between the responsible person of the manufacturer and those responsible for the relevant clinical trial in order to assess any potential impact on the trial and on the product development.

Recalls and returns

39. Procedures for retrieving investigational medicinal products and documenting this retrieval (e.g. for defective products recall, returns after trial completion, expired product return) should be in place. They should be understood by the sponsor, investigator and monitor in addition to the person(s) responsible for recalls.

Shipping – Returns – Destruction

40. Shipping, return and destruction of unused products should be carried out according to written procedures.

Shipping

41. Shipping of investigational products is conducted according to orders given by the sponsor in the shipping order.

42. Investigational medicinal products are sent to an investigator only after a two step release procedure: the release of the product after quality control ('technical green light') and the authorisation to use the product, given by the sponsor ('regulatory green light'). Both releases should be recorded and retained.

43. The packaging must ensure that the medicinal product remains in good condition during transport and storage at intermediate destinations. Any opening or tampering of the outer packaging during transport should be readily discernible.

44. The sponsor should ensure that the shipment is to be received in the required conditions and acknowledged by the right addressee.

45. A detailed inventory of the shipments made by the manufacturer should be maintained. It should particularly mention the addressees' identification.

46. Transfers of investigational medicinal products from one trial site to another should remain the exception and only be allowed in case of very expensive product, limited quantity available for clinical trials or in case of emergency. Such transfers should be covered by standard operating procedures which differentiate between the storage location of the product to be transferred (from warehouse under control of the sponsor, from the pharmacy of a trial site, or from the investigator). Should the transferred product have been stored by the investigator, not at the pharmacy, sufficient precautions and controls have to be considered prior to use at an other trial site. In most cases, the product will need to be returned to the sponsor for re-labelling and full finished product specification retesting to ensure that it is still suitable for its intended use and new release.

Returns

47. Investigational medicinal products should be returned on agreed conditions defined by the sponsor, specified in written procedures, and approved by authorized staff members.

48. Returned investigational medicinal products should be clearly identified and stored in a dedicated area. Inventory records of the returned medicinal products should be kept.

Destruction

49. The Sponsor is responsible for the destruction of unused investigational medicinal products. Investigational medicinal products should therefore not be destroyed by the manufacturer without prior written authorisation by the Sponsor.

50. Recording of destruction operations should be carried out in such a manner that all operations may be accounted for. The records should be kept by the Sponsor. This destruction should be done only after the finalisation of the clinical trial and the compilation of the final report.

51. If the manufacturer is requested to destroy the products, he should deliver a certificate of destruction or a receipt for destruction to the Sponsor. These documents should clearly identify the batches and/or patient numbers involved and the actual quantities destroyed.